established osteoarthritis and underlines the potential for prevention.

These are the outcomes in longer-term follow-up. This is, in my opinion, very important. These are new data, have not been published in full yet. There is an abstract that has been published and presented last year at the American College of Rheumatology, and in which we've gone to see what happened to the cohort of these patients years after they stopped the trial with respect to the hard clinical outcomes of the disease. When we talk about a complex issue like osteoarthritis, which sometimes is difficult to diagnose, it's difficult to relate the joint structure changes with the symptom changes, we may have difficulties in saying exactly who is osteoarthritic and who is not. So perhaps in order to be on the safe side, we should go to see the clinical endpoint, like myocardial infarction, for example, in another completely different disease. So we went to look at what happened to these patients with respect, for example, to disability and especially joint

surgery in the long run.

So in the trial of Jean-Yves Reginster, we wanted to perform a follow-up evaluation in patients that were previously in the trial to evaluate the occurrence of osteoarthritis-related joint surgery during the follow-up after the trial and after they stopped the medication, and also we assessed several secondary endpoints.

We could retrieve 83 percent of the original sample, which is good, because this was five years after the end of the study. So, overall, there is on average an eight-year observation period--three years of the trial on average, and five years of follow-up after drug discontinuation.

Patients after the trial had received standard of care. Glucosamine sulfate is not available in Belgium as a drug, and, therefore, these patients were relatively clean from this point of view. And these are the results. Actually, there were more patients undergoing knee or hip surgery in the former placebo group compared

to the glucosamine sulfate former group. And there was a reduction or a trend for a reduction of risk of 48 percent, which is not statistically significant but it is at the very limit of statistical significance, and to me it's very important given the sample size.

When we go to look for a number of knee or hip surgeries considering multiple events, the difference is similar and is really very close, if not statistically significant, and the same for the number of knee surgeries only.

It's important that you note that actually we included the hard outcomes of the disease, total knee or hip replacement, but also we included some patients who underwent other surgeries, such as joint debridement and meniscectomy--meniscectomy, of course, for degenerative meniscal disease. So it's clear that when we go to see the number of knee or hip replacement, we have exactly the same trend. It's a 44-percent decrease in risk, but this becomes less closer to significance. But I have some new data on that that I will show you.

This is important because in the two studies we've shown that we were able to prevent the number--to reduce the proportion of patients that had severe joint space narrowing. You see that there were 30 percent under placebo in the first study versus 15 percent with glucosamine sulfate, and in the second study a similar trend, 14 percent versus 5 percent, with a reasonably small number needed to treat to avoid such a worsening.

Well, we went to see what happened to these patients during the follow-up, and, actually, these patients with severe joint space narrowing had a higher chance of undergoing knee surgery during the follow-up. There was a three-fold increase in risk. So we've shown that by preventing this severe joint space narrowing, we may be preventing later on the consequences of the real clinical outcome of the disease, as we've actually indicated in our analysis.

So it's important what we did during the trial, but if we go to look to the overall eight-

year period, we can see that actually placebo over the eight years has lost a considerable amount of joint space compared to glucosamine sulfate, the formal glucosamine sulfate group, and the difference was statistically significant.

In summary, three-year treatment with crystalline glucosamine sulfate prevented osteoarthritis-related lower limb surgery, which is a clinically relevant disease outcome, during an average for the follow-up of five years. And this may be due to the structure-modifying activity achieved during the treatment and an overall delay in joint structure changes, which to me speaks very much in favor of prevention. I didn't show the data, but, in addition, the patients previously on glucosamine sulfate had a long-lasting symptomatic effect, better quality of life, and a lower utilization of health resources during the last year of the follow-up.

I would like to introduce now the talk of Professor Altman about the effects in prophylactic animal models of the disease that may support a

preventive role for the substance and on the mechanism of action. Again, I would like to make clear that these alone are not to me essential to support any claim, but they are important in that they support the clinical data that we have shown.

DR. ALTMAN: A little over ten years ago, Dr. Lequesne indicated that in structure-modifying trials, in order to develop at the time we called it chondro-protective agent, that you should really have at least two different animal models to support at least the idea. And so I'm going to give you that.

First, I'd like to just show you the structure of glucosamine. It hasn't been shown so far. This is glucosamine sulfate, obviously, and the sodium salt. It does hydrolyze in the stomach, but a fair amount of it is absorbed as a sulfate, and the sulfate is absorbed separately. I'm going to actually address that.

This is just a list of some of the trials that have been performed on animal models. I'm going to only emphasize the last two, and the first

of those Jean-Pierre Pelletier's study from Montreal.

This is a canine model of osteoarthritis. What you do is you transect the anterior cruciate ligament. It destabilizes the hind limb of the dog, and over a period of weeks, they develop osteoarthritis that becomes fairly stable at about 14 weeks, but up until 14 weeks has progressive changes. In this particular study, they examined the tissues at eight weeks. They used three different doses of glucosamine and, of course, a control group.

Just to give you an idea, I'm sure you'll hear more about this later from Dr. Witter, but in this particular model you can see the ulcer on the condyle of the animal to show you how they develop over a period of eight weeks.

Now, I want to point out that both of these studies are prophylactic studies. In the past, I've done many therapeutic studies where you allow the arthritis to develop over a period of weeks and then you start to treat. In both of

these studies that I'm talking about, the treatment was started immediately after surgery. So we're getting at the onset of the illness.

The second slide from Dr. Pelletier's group shows the osteophytes that occur along the joint margin that are similar to human osteoarthritis. Now, the canine model is actually a very good model for human disease. Of course, there's nothing that really is completely the same as human disease. The rabbit model that I did is a little bit less specific.

This shows you the femoral condyles of the osteoarthritic and the treated animals, showing you the ulcers up above that were not as great as, certainly lesser size in both the condyles and the tibial plateaus of these dogs.

And the histology. The question was asked earlier: How do you know whether the proteoglycans are of proper size? That can be done, and we used to do that. We now just look at safranin-O staining. Safranin-O stains the proteoglycan molecule, the aggregate proteoglycan molecule, and

you see there's a loss of safranin-O staining in the osteoarthritic model. There's a fast green counter-stain to point up the rest of the tissue. The other things that are looked for is surface disruption. You can see significant surface disruption here, a lesser degree here. Cellularity is actually decreased in part of the tissue here, the cellularities here. This doesn't show the tide mark, and I'll show that in the rabbit model.

In any case, Dr. Pelletier also looked at--Drs. Pelletier, I guess I should say, also looked at the amount of stromelysin that was present, and the amount of metalloproteinase that was present in both, in the membrane was actually decreased where the amount of amount of metalloproteinase in the cartilage was not significantly changed, actually. And this is consistent with some of the others that's been presented.

Because of time constraints, I'm going to quickly go into the study that I performed, and this is a lapine model, a rabbit model, where we had four different groups--two different dosing

groups, and, of course, a placebo osteoarthritic group and a placebo normal group.

We have done other studies with glucosamine looking at it in normal cartilage, and it does not seem to change the structure of normal cartilage, at least in the animal model.

Now, the difference in the gross anatomy here is that we used what's called a Meecham stain, which is just india ink that's applied to the surface of the cartilage and then wiped off so that you can get a decent picture. And you can see the normal doesn't retain any india ink; the osteoarthritic contains considerable india ink, showing a lot of the surface disruption. And you can see in both the low-dose and the high-dose glucosamine-treated animals that they had very little in the way of retention of the india ink.

Histologically, it supports the same thing here. The safranin-O is much more intense in stain. You can see the tide marks intact here. The tide mark is disrupted here. It's more normal in both the low- and high-treated group that retain

the safranin-O, retain the surface, and so on this model the glucosamine was actually preventive of disease.

Now, I did want to go over just a couple of things on mechanisms of action. For instance, there's a considerable amount of data showing that there are anabolic effects in the cartilage for proteoglycans and some of the minor sugars, such as perlecan, in cartilage.

Secondly, there is an anti-catabolic studies showing there's a decreased amount of actual functional stromelysin in the tissue as well as that the glucosamine decreases the aggrecanase, and this is by John Sandy, one of the most critical people that I've encountered in my editorial work.

One of the things here--this is a culture medium; this is where you take interleukin-1 and put it into cultured chondrocytes. Osteoarthritis is very much an interleukin-1--could be arguably an interleukin-1-driven disease. Even though TNF is there, it's much more dependent on interleukin-1. And in this particular study, you can see that the

amount of proteoglycan is retained with increasing doses of glucosamine and the amount of proteoglycan that seeps out into the culture medium decreases with increasing doses.

Now we're going to get into the concept of inflammation. The term is "osteoarthritis," and Dr. Abramson and Dr. Pelletier have published a very nice editorial in Arthritis and Rheumatism pointing out that osteoarthritis is really an inflammatory disease. And this is some of the evidence for it, that interleukin-1 does induce prostaglandins and nitric oxide release from chondrocytes. Prostaglandins are, of course, the inflammatory mediators. Nitric oxide may have something to do with the ability of the chondrocyte to survive. It may stimulate programmed cell death.

In both of these, you see a reduction with the glucosamine and a dose/response relationship, and these are doses, by the way, that are achievable with the oral 1500 milligrams.

Going a little but upstream from the

prostaglandins to the enzyme that actually produces the prostaglandins, IL-1-induced COX-2, cyclo-oxygenase 2, as well as inducible nitric oxide synthetase, are reduced--are increased with osteoarthritis and their expression is actually decreased with the amount of--with administration of glucosamine.

Did I skip one there? No.

Now we're moving further upstream, and here we see that interleukin-1 reduces NF-kappa B activation. And this is important because now we're starting to get into the idea that we're moving upstream in the cell and where the glucosamine may be actually having its function. And in this particular study, you can see that the amount of interleukin-1-stimulated cartilage degradation is reduced with the glucosamine. And that can be demonstrated very nicely with some staining that you can see here with the basal cell amount of NF-kappa B, the stimulation with IL-1 beta, and the suppression that you can get with the glucosamine, no effect with glucosamine alone, and

partial suppression with the IL-1 beta plus the glucosamine.

That was from one study. This is from a different study indicating that COX-2 messenger is actually reduced in chondrocytes that are stimulated with interleukin-1 beta, again pointing out reduction in the inflammatory mediators.

So what we've come to is a hypothesis that the interleukin-1 phenomenon that goes through a second messenger to stimulate the chromosome to produce the prostaglandins is blocked by nonsteroidal anti-inflammatory drugs, but this part doesn't seem to be. Whereas, if we go to glucosamine and paralyze the NF-kappa B, at least the 50 molecular weight product at this level, then we interfere with the production of the prostaglandins as well as the MMPs, et cetera.

There's just one last thing I wanted to point out, and that is the question as to whether the glucosamine hydrochloride or the glucosamine sulfate makes a difference. There's really not a lot of information on this sulfate, but there's two

studies that have come out fairly recently that have indicated that the amount of serum sulfate is actually increased when you use glucosamine sulfate. And here's one of those studies, the first of them, and this is the second of them, indicating that--this is from Marcel Nimni's group showing that when you increase the amount of oral intake of glucosamine, you actually increase serum sulfate. And serum sulfate in this case is being a driver for the production of proteoglycans.

Thank you very much.

DR. ROVATI: I'm afraid I have to apologize because, besides suffering my awful Italian accent, you have also to face my bad memory, and I forgot to show you a very important slide, which is actually this one, because as I told you, we performed the follow-up evaluation in the Reginster study, but I forgot to tell you that we just recently performed the same in the Pavelka study. And this is clearly unpublished information. The data came out around four weeks ago, and we just submitted an abstract this year to

American College of Rheumatology.

This time we took 136 patients who had--we could retrieve 136 patients who had been in the trial for at least 12 months, which were 80 percent of the original cohort with these characteristics, so pretty high. Median duration of follow-up also in this case with standard of care after starting medication withdrawal was for five years. And I told you that in the Reginster study we could not see a significant difference in the number of patients with total knee replacement, which is the natural endpoint of this follow-up. But we were able to see it in the Pavelka study. You see that patients in the former placebo group had a 16-percent incidence of knee replacement--well, there were 16 percent patients undergoing knee replacement versus 4 percent, which is a decreasing risk of 73 percent, which is statistically significant.

I apologize for that, and I will go immediately to the last information that I would like to provide you today.

There are several glucosamine formulations out there. We believe that there are not enough data to support any claim, either this claim or any other claim, with these other formulations of other glucosamine salts simply because we do not have the evidence or simply because the evidence is just with the sulfate.

Also, while we have evidence, some evidence that chondroitin sulfate may work in osteoarthritis, as was noted in the previous discussion there was actually no hint of any activity of the glucosamine and chondroitin combination, either as an additive or synergistic or perhaps detrimental effect, as it may be. And this is because, I believe, it may not--this formulation may not share the same pharmacological clinical quality or PK properties of the substance that has been used so far.

Pharmacology is not a problem because you can always give to the animals as much glucosamine as you want in any salt or formulation. But the problem may be clinical and actually the only

evidence is with sulfate, crystalline sulfate, as I told you, quality, and PK is also, in my opinion, important.

With respect to treatment, I want to make clear that in the Lancet study, we were saying that the results cannot be generalized to other glucosamine products or mixtures with our compound. And I want to underline that this was a statement that was specifically requested by the reviewers because they were scared that we were generalizing it to thousands of dietary supplements in this respect. And the same statement is present in the Archives of Internal Medicine.

Quality consideration, why quality is important. Well, this formulation is regulated actually as a prescription drug in Europe and in several other countries, and so it's subject to strict quality controls. You may know that there are studies, one recently in the Journal of Rheumatology by Russell, that showed that out of 14 nutritional supplement formulations of glucosamine sulfate available in North America, only two

contain over 80 percent of the labeled glucosamine content, and for 12 formulations the stated amount ranged between 41 and 66 percent only. And these data just follow another observation, a similar observation from the University of Maryland published three or four years ago.

PK is also important because, unfortunately, the knowledge about the glucosamine PK has been limited by the poor sensitivity and specificity of the available cold chemical methods. And this, unfortunately, favored a lot of confusion in this respect, because if you cannot prove exactly the PK pattern or the PK profile of the compound, it's easy to make any claim for anything.

Luckily, very recently we were able to develop a liquid chromatography mass spectrometry detection that was validated for the determination finally of glucosamine in plasma--it was tough to develop--and allowed to study the oral bioavailability and disproportionality of the original formulation in man. And, again, these are very recent data submitted this year to the

American College of Rheumatology meeting. And I'll just show you the data, but you can actually follow very well the time course profile of glucosamine in plasma, and you can see a dose/response increase 750 or 1.5 grams once daily. It's not linear when you go over 1.5 grams, so also this is important to take into account with respect to the dose. You can calculate the half-life of elimination and support the once-daily administration that was used in the clinical trial.

Very importantly, the level that we find with a 1500-milligram dose is in the range of those that are effective *in vitro* in the chondrocyte cultures that Professor Altman has shown to you.

About significant scientific agreement, of course, we have to rely mainly on the available practice guidelines. This has been mentioned before. The very recent EULAR practice guidelines on knee osteoarthritis, this is clearly for treatment. It's not for prevention. But it's about the role of glucosamine sulfate in osteoarthritis. Glucosamine sulfate was scored the

highest level of evidence, 1A, and the highest trend of the recommendation, A. Out of 34 pharmacological and non-pharmacological modalities, this was attributed only to six of them.

In addition, glucosamine sulfate was attributed highest median quality score for trials performed, 24 out of a maximum 28, and among the highest effect size versus placebo.

What about the American College of Rheumatology practice guidelines? We have the two sides of the Atlantic, of course, and both are exactly the same as important. The problem with the American College of Rheumatology guidelines is that the last version was published in September 2000, prior to the publication of the two long-term studies, prior to the Cochrane Review, prior to the last review. And this expert committee, four experts, in which Professor Altman was included, was unable to reach a conclusion or recommendation on glucosamine. But already one year after, one of the members of the committee, Marc Hochberg, was publishing a significant paper entitled "What a

Difference a Year Makes," a reflection on his recommendation, saying that the documented efficacy of the substance requires us to reassess the use of glucosamine as a first-line agent, at least for patients with knee OA who have mild to moderate disease, which, again, goes in the direction of treatment and possibly of prevention.

Safety, all systematic reviews and meta-analyses support the safety of glucosamine sulfate in humans, and as you can easily check, the adverse event profile is really very safe, 6 percent to 15 percent incidence of patients with adverse events, dropouts in less than 4 percent, no significant difference with placebo in any trial, but significant advantage, of course, over conventional nonsteroidal anti-inflammatory drugs when you compare the drug or the compound for the treatment of symptoms of osteoarthritis.

In the two long-term trials, as you may know, the safety of the substance was similar to that of placebo. And I want to underline that being regulated as a prescription drug in over 40

countries of the world, we have to issue regular, periodic safety update reports according to ICH guidelines, and information that I gathered from here over the last five or six years estimated that out of over 30 million patients per month, there were only 200 spontaneous adverse reaction reports, with no safety signals at all.

So I would like to conclude saying that I believe we have tried to show you evidence on how the treatment data in high-quality, long-term clinical trials with glucosamine sulfate may support the claim for prevention that we've gone through. There are several clinical indications. We recognize that there is no study of prevention, and perhaps this will be difficult to obtain with anything in the near future. But there are several hints from the data published that suggest that the substance may prevent osteoarthritis, as I showed, and also the animal and mechanism-of-action models, although not enough alone, support very well the clinical data.

I thank you very much for your attention.

DR. MILLER: Thank you, Dr. Rovati.

Comments of questions?

DR. CUSH: You showed data from both trials on the need for replacement surgery of the hip or knee, although those trials were originally designed to study indexed knees. Were the same statistics arrived at when you only looked at the indexed knee? And did you have any--were any of those replacements involving contralateral knees or hips?

DR. ROVATI: Yes. In the Reginster study, actually, there was not much difference between the signal joint or the contralateral joint. In the Pavelka study, I must say that we did not perform the analysis yet because these are very new data.

DR. MILLER: Dr. Downer?

DR. DOWNER: You mentioned that there were 209 spontaneous adverse reactions. Could you clarify and tell us a little bit more what they were?

DR. ROVATI: They were mainly mild GI complaints about the patients, which are more or

less the same that we see in clinical trials, although at a very low level and similar to placebo. My report is that these patients are used to be careful to GI systems when they take anti-rheumatic medication or prevention of supplement or whatever, and sometimes they report that.

Certainly there was no other signal for any specific safety issue. For example, there was nothing with respect to diabetes, and you know that there are now several studies in humans showing that the pharmacological data on insulin sensitivity obtained in animals may not be replicated in humans. And, actually, in the Pavelka trial, for example, there were four patients developing diabetes during the study--one was on glucosamine but three were on placebo.

DR. DOWNER: I have a follow-up question to that. There were some significant improvements in the data you presented, and I'm wondering if there were any confounding variables, such as, did you see an improvement in weight, for example? Could that have impacted on some of the information

you have presented?

DR. ROVATI: No, there was no other modification in any general health status, nothing on weight, nothing on other diseases, nothing on heart rate, blood pressure--nothing at all.

DR. DOWNER: Are you saying nothing because you did look at these parameters?

DR. ROVATI: We did look exactly at this.

DR. DOWNER: Okay.

DR. ROVATI: Weight, blood pressure, and heart rate. And, of course, we looked at any worsening of co-existing diseases that in this healthy population may be present.

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: I was just curious with the elevations of the sulfate that Dr. Altman showed in the plasma. When you look at your database--I'm sorry, on uric acid levels. I'm just wondering if there are any effects as an organic (?) and whether in the populations you've treated you've seen any effect through uric acid?

DR. ROVATI: I must say that we did not

look at that, so I don't know. I think there is nothing, but we did not look specifically at that.

DR. MILLER: Dr. Lane?

DR. LANE: Yes, I'm curious about a couple of the endpoints in the Reginster study and your other study. You showed that the joint space did not--the width of the joint space did not deteriorate, in fact, it appeared to increase in the Reginster study. What about other individual radiographic features of OA, such as osteophytes?

DR. ROVATI: Okay. It was actually not increasing in average in the Reginster population. There was a non-significant decrease of 0.7 millimeters, if I remember correctly. It was a bit less in intention-to-treat population of the Pavelka patients. But, clearly, there were some patients who tended to increase, as Dr. Felson mentioned before, but these were a minority.

And, sorry, your other question was?

DR. LANE: What about osteophytes?

DR. ROVATI: Okay. No, we didn't look at that in the Reginster trial because the X-rays were

sent for digitalization to London in the unit of Jane Decker, and we could not look at that afterwards, while with the Pavelka study, the analyses were performed by the investigators themselves and so they could look also at this.

DR. LANE: One more question. I'm always interested in osteoarthritis if the patients were acting the same in the placebo and the treatment group. Are there any measures of activity level, you know, what the patients were doing, you know, walking, running? Was it the same, their daily activities?

DR. ROVATI: We specifically asked at enrollment of the entry criteria that the patients should have not undergone any particular heavy activity, and also any physiotherapy or exercise had to be present and standardized before the entry into the trial. And in this respect, the two groups in both studies were very much comparable.

DR. LANE: Thank you.

DR. ROVATI: Dr. Felson?

DR. FELSON: Lovely data-based review with

a lot of data, which I know you've been very involved in. The issue here is prevention, and you were careful, I thought, and prudent about being very clear and accurate about what your data showed with respect to that. I wanted to go at that question a little bit farther in terms of the contralateral knee, which you talked about some.

You mentioned that the contralateral knee tended to have pretty large joint space at baseline in both of the studies. The issue here is whether the contralateral knee had OA, because if that were the case, then there would be evidence that this was a treatment in established OA as opposed to a treatment of a joint that was unaffected.

Most people with knee OA, 60 percent roughly, have bilateral disease, not unilateral disease. So do you know the Kellgren and Lawrence grade of the contralateral knee?

DR. ROVATI: Yes, it's an excellent question, of course, and we looked for minor signs of osteoarthritis and--minor signs of osteoarthritis such as initial doubtful

osteophytes, I may say, that were present in most of these patients.

With respect to Kellgren and Lawrence, we were not able to give to them a Grade 2, but there were minor signs of osteoarthritis.

DR. FELSON: So remembering, just for the committee, that by the time you get radiographic disease, radiographic disease is a fairly late structural finding of osteoarthritis. So the fact that there were small osteophytes in most of the contralateral joints suggests that there was existent disease in those contralateral joints.

Now, that begs the question of sort of when is incident disease, which is a very difficult question that we could probably spend another week on and not get the answer to. But in another recent trial, one that was presented at ACR, of doxycycline, another potential remittive or disease-modifying therapy, in which there was a great attempt to get unaffected contralateral knees, they made a very strong comment at the end of the day that they were pretty much unable to get

unaffected contralateral knees, that, in fact, when they looked closely at the contralateral knees, they all had some measure of osteoarthritis.

So for the purposes of thinking about prevention, I would just take those arguments into account perhaps.

DR. ROVATI: You're totally correct. As I was saying, probably these patients could be classified as Kellgren and Lawrence Grade 1, which is doubtful osteoarthritis. I agree with you.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: I think Dr. Felson has addressed the issue that I was concerned about, and that was the two studies where you used the data with respect to the contralateral knee, and the Pavelka study shows no significant difference. So I assume you can discard that.

And if we look at the Reginster study, the placebo group seems to be advancing at a much more rapid rate than what's been referred to as the normal group. So can we describe that as a normal knee? Can we use that as a normal knee joint?

DR. ROVATI: Yes, thank you very much. It's an excellent question. Actually, these data in the Reginster trial are consistent with the quartile analysis that I showed. The patients that were--in a signal joint that were progressing were those in a better joint state at enrollment. And so the contralateral knee, at least in this particular cohort, that had an even better preserved joint space, was progressing even more. So this is consistent throughout this patient population.

With respect to the Pavelka trial, you're totally correct, and I have underlined that the data were not significant. But you also have to note that although the difference with placebo in the Pavelka trial was of the same magnitude as in the Reginster trial, they tended to progress a bit less. And, actually, we noted--and it's published--that these patients were a bit leaner than in the Reginster population. And overweight may be a risk factor, and this is why we may see more progression and more prevention of disease in the Reginster

trial than in the Pavelka study.

DR. KRINSKY: Thank you.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: In your pharmacokinetic studies, you reach peak plasma levels rather quickly. Do you know--and it drops rather quickly. Do you know anything about the distribution of this compound in the target tissue?

DR. ROVATI: Yes. This, of course, we could not do yet in humans. We are trying to validate the method, at least in synovial fluid, to see what we have there. But it's not been developed yet.

We have early animal data that have been reported before by the previous petitioner in which we uniformly labeled glucosamine with C14 on a carbon ring. And, actually, with autoradiography, after administering the compound by the oral route and taking autoradiography of the intact rat, we saw that the compound was concentrating--well, was very much in the liver because, of course, the liver represents a first--has a first-pass effect,

and then was concentrated specifically in the joint areas that we could analyze. But, of course, we have no data in humans. This is very clear.

DR. MEHENDALE: Can you give us some idea what percent of either dose or relationship to plasma levels might be found at the cartilage tissue?

DR. ROVATI: We currently estimate, based on this new data, that the absolute bioavailability, although we do not have an absolute bioavailability yet, is around 20 to 30 percent of the oral dose. And the previous animal studies have shown that, compared to blood, it concentrates five times more in the cartilage with respect to the blood itself or other organs.

DR. MEHENDALE: I have a question about the *in vitro* studies where you showed--Dr. Altman's studies, where he showed effects on number of signaling molecules. My earlier question relates to this, to see the levels that he used in these *in vitro* studies to show effects on signaling events, how they might relate to the levels you find *in*

vivo. I don't know if you might have some information that you might shed some light on.

DR. ROVATI: Probably I was very quick on that, but the actual levels that we found in plasma, especially if you consider that, according to our early data, the compound concentrate in the cartilage, they are pretty much in line with what Dr. Altman has shown as an effective concentration at the chondrocyte level in culture.

DR. MEHENDALE: And one more question. I wonder if you know what the effects might be in normal tissue then with those levels on the signaling events in the cartilage tissue.

DR. ROVATI: Dr. Altman, do you want to take that?

DR. ALTMAN: Go ahead.

DR. ROVATI: Actually, the data that Altman has presented to you, there are two particular studies as shown *in vitro*--one which was from an independent Spanish group and one which was obtained in our lab confirming the findings. And, actually, the results are very much superimposable,

but the real difference is that they used osteoarthritic chondrocytes taken from osteoarthritis patients, and we took an absolutely normal chondrocyte from animals. So the effect, when you stimulate the chondrocyte with a strong pathogenic factor such as interleukin-1, seems to be the same irrespectively whether the chondrocyte is already osteoarthritic or is normal.

DR. MEHENDALE: This applies to COX, INOS, as well as signaling molecules, NF-kB--

DR. ROVATI: Exactly.

DR. MEHENDALE: Uniformly on all of those?

DR. ROVATI: Exactly, because we believe that the main pharmacological activity of the compound is actually to inhibit or reduce the translocation of active NF-kappa B that then stimulates the expression of COX-2, INOS, metalloproteinases and so forth, and we actually so the same in healthy or osteoarthritic chondrocytes.

DR. MEHENDALE: Right. To extend this a step further, I wonder what the implications might be to a normal tissue, normal cartilage, upon

repeated decreases in these molecules, obviously in the absence of any disease.

DR. ROVATI: Yes, it's an excellent comment, of course. We believe that there is--as was said also by the previous speaker, by the previous petitioner, when you simply administer glucosamine to healthy chondrocytes or healthy animals, you simply see no effect or at least no effect that we can detect. The only effect you see when you stimulate, for example, *in vitro* even the healthy chondrocyte with a pathogenetic factor. So that's why we believe that the preventive issue may be supported by that, because when the pathogenetic factor enters into play, then you can prevent it from exerting its effects. But in the normal cartilage, in normal animals, you actually have nothing.

DR. MEHENDALE: One limitation of those *in vitro* studies, of course, we don't have an opportunity to look at repeated exposures on normal tissues. And, therefore, we are kind of walking an unknown bridge, so to speak, when we translate into

in vivo effects.

DR. ROVATI: I take your point.

DR. MILLER: Dr. Zeisel?

DR. ZEISEL: Getting back to Dr. Felson's point about contralateral knee not necessarily being normal, as a non-rheumatologist, could you help me? Of the 20 to 25 members of this panel who do not think they have arthritis, how many of them have abnormal osteophytes, for instance, on their knees?

DR. LANE: How many have had their knee X-rayed?

DR. ZEISEL: Well, how many would you guess from your look at normal individuals who don't come in with a complaint of osteoarthritis?

DR. FELSON: That's a really--it's not a hard question to answer, but its interpretation is pretty tough. So I can tell you, as the head of the Framingham Osteoarthritis Study, a sub-study of the Framingham Heart Study, in which we've just obtained MRIs on a lot of normal people age 45 and over, that nearly 100 percent of knees of people

age 45 and over have tiny, or larger, osteophytes, many of which are not visible on the X-ray.

One of the reasons we use the X-ray as our way of defining disease is mostly historical, but also because it actually provides a threshold level of size of osteophyte that tends to help us distinguish between those with pain and those without pain reasonably well. So those tiny little things that we see on the MRI usually aren't the threshold level above which--I don't know if there's meaning to the definition. I'm not sure there is, but if there is, that would be it.

There's a different question here, though, which is: Is prevention for a health claim, which I think is probably what we're supposed to talk about here, the prevention of contralateral disease in someone who has unilateral disease, or is it prevention of the new onset of disease in someone who doesn't have disease at all? And I think we're increasingly aware of the fact that this is a bilateral and often systemic process and that the presence of clinical disease in one joint is either

a harbinger of or goes along with clinical disease in its contralateral partner. And I think it would be--I don't think these are people who have contralateral joints which are the same as your joints, assuming that you don't--that you have those tiny little osteophytes that we all have.

DR. ZEISEL: Okay. But, again, the point I am thinking about is that if almost 100 percent of the members of this panel have pathology on their knees which would not have been there when they were probably 17 years old and we're dealing with chronic diseases that have a continuum, it is a leap of faith both to argue that they are the same as what the person has in the osteoarthritis, but it's also a leap of faith to argue that they aren't part of the early continuum, that if you followed those individuals from the Framingham Study and looked at them 15 years later, many of the ones who have more osteophytes went on to have the early stigmata of osteoarthritis.

And so if that's the case, then the contralateral knee argument that's being made is as

close as you can get to extracting data that's clinically already there that may be useful.

DR. MILLER: Actually, another way of putting it--and it's a matter that we can discuss tomorrow--is in order to--one of the questions we need to deal with is what is the kind of data that would be needed in order to demonstrate that a prevention claim can be made. And it seems to me that the big argument is what constitutes the baseline. I wouldn't call it normality, but what constitutes the baseline. And that should be one of the questions we ought to be discussing tomorrow.

Dr. Russell?

T7 DR. RUSSELL: I had questions more or less along the same lines that have been discussed now.

DR. MILLER: Dr. Callery?

DR. CALLERY: This is a question back to the compound that you've been discussing, and thank you for pointing out that most of the studies done were done with compounds that were not well characterized and probably not what they said they

were in the process. But let me ask a question about your compound in particular.

If you had an equal molar amount of your complex versus pure glucosamine free base or glucosamine hydrochloride, would you expect a better response from your compound?

DR. ROVATI: There is certainly the factor of sulfates, and as Professor Altman mentioned, we do not know exactly how much sulfates are important. They're clearly important in the metabolism of cartilage. Whether they significantly increase the pharmacological activity of glucosamine sulfate is not known at present. The only data we have is, again, the clinical data with glucosamine sulfate.

So I think that your point is well taken. So if you exclude the sulfates and you provide the primary active ingredient, which is clearly glucosamine, I think you should--you may get similar effects, as long as this different formulation has the same pharmacokinetic properties and as long as you can actually, since there is

this uncertainty about sulfate, you show some kind of therapeutic equivalence or something, some hints that lead you to think that the effects may be the same.

DR. MILLER: Dr. Blonz?

DR. BLONZ: I think that the European regulation as a drug is informative. As we get closer to the lunch break, I want to step back a little bit and talk about the substance itself. We're talking about food here. We're not dealing with drugs. And we are talking about putting this in the food supply.

Now, according to the Federal Food, Drug, and Cosmetic Act, for something to be added it's got to be a food. It's got to be a food substance. And according to your petition, we're talking about a substance that's a vitamin, mineral, herb, or other similar nutritional substance, specifically food or a component of food.

So what specific food or component of food do you find crystalline glucosamine sulfate?

DR. ROVATI: You do not find crystalline

glucosamine sulfate. You find glucosamine or you find the glucosamine sulfate incorporated in the tissues in any food that contains cartilage or perhaps--well, connective tissues.

It's clear that the regulations in the U.S. and in Europe are quite different in this respect because the U.S. has a specific regulation of food supplements or dietary supplements that are regulated as a drug in Europe because there is not any provision for food--they're starting to arrive, but there's not any provision. So whatever you show in Europe, automatically you are a drug. You do not have the option of having a food supplement.

DR. MILLER: Dr. Cush?

DR. CUSH: I just want to make the statement that I think Dr. Felson's comments are very helpful, and we do know that X-rays will show progressive evidence of osteoarthritic change in a population as it ages. But it's also important we teach to our students and to primary care doctors that there's a real disconnect between symptoms and X-rays. And, hence, you know, making decisions

solely based on radiographic and imaging studies about joint space narrowing and whatnot may not--is still a big leap to actually symptomatic disease.

DR. MILLER: Dr. Kale?

DR. ROVATI: Can I comment on that, Dr. Miller?

DR. MILLER: Sure.

DR. ROVATI: You're perfectly right. It's clear that symptoms and structure do not go in the same direction, at least in the early stages. When you then arrive to the point of joint surgery, you have a severely damaged joint and you have symptoms.

But this is absolutely extremely important, and actually I did not show about the quartile analysis in the Reginster cohort showed that, while only those more (?) were progressing in joint space loss, both were progressing in symptoms and the compound was effective in both on the symptoms of the disease. So it's clearly something which is divergent. Perhaps until the very late stage when the two go to the endpoint or

final clinical outcome.

DR. MILLER: Dr. Kale?

DR. KALE: A number of comments, but most recently, the comment made by Dr. Miller forces me to ask what may be a theological question, and that is: Who are the proper subjects for this product? If we can't agree when osteoarthritis begins in an adult and if the data that you've collected in your studies looking at now MRI scans suggests that disease is virtually everywhere, then where is it not everywhere, radiographically or otherwise? Who would serve as appropriate subject for this nutritional product? Would it be something like a vaccination, we start at birth? When would one start?

DR. ROVATI: Certainly the therapeutic data available support the fact that the substance is particularly effective in mild to moderate osteoarthritis. This is clear, although the symptoms can be treated also in more severe stages in the short-term clinical trials, reviewed in the meta-analysis support that. I think I tried to

show you that this mild osteoarthritis can be probably brought a little backwards and we can treat patients--or we can supplement subjects that are at risk of osteoarthritis.

DR. KALE: The question is how do you determine who--everyone's at risk, which is why you end up vaccinating everybody. Everybody's at risk, because we all are. How do you decide? And if the issue here is prevention, then the question is preventing when, in whom, how?

DR. ROVATI: It's an excellent question. I'm not that expert to reply precisely to that. I would say patients who may be at risk because of physical activity, because of weight, such as obesity, or simply because, for example, in an X-ray they have minimal signs of osteoarthritis which is not yet clinically significant and this may be helpful.

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: These are difficult questions, and I guess as a rheumatologist it's important to frame this in the context of where the

field is. And for those people who are not rheumatologists, the NIH, as we heard very early on, is spending millions of dollars to study 5,000 people to, in essence, address this kind of question, people with very early disease, what happens to them over five years or longer, with the presumption being that most do very well and don't need any intervention of prevention. But the answer is the fact is that the field--these are unknowns in the field. So I think what we're grappling with is how do we pretend to know the answer today when we're not going to, at least academically, to the extent that the OA initiative can address that, won't know that for five years.

And I guess that raises a question or a clarification for me as we each struggle with this that does touch on regulatory. Here we have a compound that's synthesized, that has a mode of action that looks like a drug, inhibits NF-kappa B like corticosteroids do, that now would be--it is a drug in Europe, and then we are--so if we were addressing this as a drug in the U.S. across the

street at CDER, we would be asking for the clinical evidence that it prevents.

So how do we wear two hats here? And I guess this is kind of a regulatory question. Can it be a food here where we apply a different set of standards than if this meeting were happening in this hotel, you know, two years from now, if you filed an IND or something, or an NDA, would the discussion be different and should it be different? You know, this is where I think a lot of us are trying to understand the process at this committee rather than at the arthritis--

DR. MILLER: The decision concerning how this is to be regulated is made by the agency, as far as I can tell. Our concern is the science, irrespective whether it be regulated as a drug or as a food. The difference is that the law defines foods--defines supplements as foods, and that complicates the issue, but not for us. Our issue, the issue that we're supposed to deal with is: Is there sufficient data to support the idea that this prevents osteoarthritis? And if not, what data

would be needed in order to do it? That's the kind of question--how that ultimately gets used is a matter for the agency and the lawyers deal with. That's something we just can't--I hope to God we don't ever get involved in.

[Laughter.]

DR. MILLER: Nothing personal to my friends in the agency.

Dr. Espinoza?

DR. ESPINOZA: I was wondering, since this compound also relieved pain, if there is any data about its use in other populations, in younger patients, rheumatism, fibromyalgia, especially in Europe.

DR. ROVATI: There are some early data on chondromalacia of the patella, but I would be reluctant to take them as evidence of their activity in this kind of disease because these were really early data produced over 20 years ago when clinical trials were clearly not of the same standard as of today. So today there is no new study in this respect.

DR. MILLER: Dr. Lund?

DR. LUND: With regard to the fact that we all show some signs of this disease in our joints, to what extent does genetic predisposition to this disease play a role? And is this a treatment for those with a genetic predisposition to the disease?

DR. ROVATI: I hope this is a question for the experts.

[Laughter.]

DR. LUND: Well, I'm just curious as to whether in your studies with regard to the longitudinal studies that have been performed, whether you got to the question of the genetics of the disease, basically.

DR. ROVATI: I was joking. It's an excellent point, of course, and, unfortunately, we didn't perform any genetics in any study, I must say.

DR. MILLER: Do you want to answer that question?

DR. FELSON: No, I don't.

[Laughter.]

DR. MILLER: Then you wait. You're not going to be helpful, you wait.

Dr. Harris?

DR. HARRIS: Yes, the question just posed I think is a very important one. In fact, it was one that I was going to pose, so I think we are basically on the same wavelength here. But not only do we have to worry about genetic predisposition, we also have to worry about states of development. And I just wondered, in your studies that you performed or the literature has now documented, is there any evidence of glucosamine may be more beneficial to the younger set as opposed to the older set? And do we have to make adjustments in that case to dosage or quantity that we need to achieve the effects we're looking for?

DR. ROVATI: The two studies, the two long-term studies, were pretty homogeneous with respect to the age of the subjects. They had on average 65 years, and the limits were actually between 55 and probably something more to 70.

Actually, one of the entry criteria was patients over 50 years as required for the guidelines for treatment of osteoarthritis.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: Earlier, in response to a question, you included obese people as a possible population. A significant number of these are going to have diabetes or maybe already have in unawareness. And do you know the effect of this compound in such individuals?

DR. ROVATI: As I was mentioning before, there is currently no evidence in humans that glucosamine, any form of glucosamine, may precipitate diabetes in some way. Actually, we published a letter in the Lancet three or four years ago in which we were examining the blood levels of the patients in some of the earlier studies, short term, and in the long-term trial of Reginster.

While in the long-term trial of Reginster we had no patients with hyperglycemia at baseline and, therefore, I cannot answer to this question,

we saw, if anything, a decrease, a trend for a decrease in the glucose blood levels.

We examined the facts in some short-term studies. We had a reasonable amount of patients with hyperglycemia although they were not diagnosed as diabetic. And also in this case, we had no increase in fasting blood glucose.

DR. MEHENDALE: Do you have any information on insulin levels in these people who take this drug?

DR. ROVATI: We do not have from these trials. This was not scheduled. This is something that came out after the trials were designed. But I would like to mention one study that should be taken carefully for the reasons that I said before, because this is actually something done with a supplement of glucosamine hydrochloride and chondroitin sulfate, and they administered the substance for three months, if I'm correct, to patients with Type II diabetes, and they looked at insulin, they looked at glycated hemoglobin, and they found no change compared to placebo and no

progression in anything.

DR. MILLER: Dr. Felson?

DR. FELSON: [Inaudible, off microphone.]

DR. MILLER: Dr. Downer?

DR. DOWNER: You mentioned animal sources, particularly cartilage, as a dietary source for this. Would it be fair to say that vegans who are not physically active may be at greater risk for OA?

DR. ROVATI: I'm afraid I did not catch exactly--

DR. DOWNER: The vegans, the strict vegetarians, those who do not include animal products cartilage.

DR. ROVATI: I don't know if there is any epidemiological data on that. Perhaps Dr. Abramson and Dr. Felson...

[Inaudible comment off microphone.]

DR. DOWNER: You would be surprised. I have obese vegan patients. You would be very surprised. I think animal products have a role.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: This is not for Dr. Rovati, just for information. Two things.

One, in the Framingham Study that you've mentioned, are they, in fact, questioning whether the people are taking glucosamine and/or chondroitin sulfate?

DR. FELSON: Yes, but there's a lot of confounding by indication. You know, you can't tie--people take glucosamine because they have joint pain, and so there's likely to be an association of disease with glucosamine use. So you can't really test the preventive issue there.

There are ways now you could sort of get at that, propensity score stuff, but, you know, we haven't messed with that yet.

DR. KRINSKY: Okay. Thank you.

The other question is just informational. We have these written comments from Nutramax Laboratories, and I don't understand how they relate to our committee work. Were they solicited by the FDA or were they just free contributions?

MS. REED: They were just submitted.

DR. KRINSKY: Okay. Thank you.

DR. MILLER: I think at this point it's time for lunch. Thank you very much.

Lunch for the members of the committee and guest speakers is in the room next door, the break room. For everybody else, you're on your own.

We will return at 1:30 promptly to begin the session.

[Luncheon recess at 12:21 p.m.]

AFTERNOON SESSION

[1:30 p.m.]

DR. MILLER: This is the afternoon session. There are a couple of announcements that I have to make, and clarifications.

First of all, for the record, Mr. Michael McGuffin, who is a member of the Supplements Subcommittee and was supposed to join this committee for this discussion is unable to join us.

Second of all, I've been reminded that the phrase "prevention" is a term of art in drugs and "risk reduction" is a term of art in foods. And, therefore, we ought to be talking about risk reduction and not prevention. Since I've been doing that more than anybody else, I suppose I have to say mea culpa.

And, lastly, when you've finished talking using the microphones, please remember to turn them off. It confuses the AV person who gets too much extraneous noise.

This afternoon we begin with a presentation of Dr. Lee Simon of Harvard University

on the current state of etiology of osteoarthritis and modifiable risk factors. Dr. Simon?

DR. SIMON: Thank you. Good afternoon. I know everybody is bright-eyed and bushy-tailed back from lunch. I'm first up to be able to keep you awake for the next half-hour or so.

I am a rheumatologist by training, and for perspective's sake, I'd just like to make clear that I've been involved in this debate in that I was the former Division Director of the Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products in CDER, where I just left about five months ago. Furthermore, although my disclaimer is quite clear that I have no actual involvement in any company, pharmaceutical or nutraceutical or otherwise related to glucosamine or its congeners, I do have involvement in drug development consulting related to other companies in the field of rheumatology, particularly relating to disease-modifying agents as well as nonsteroidal anti-inflammatory drugs, which some of you actually know quite well.

I was charged by the organizers--and I want to give my thanks to them for asking me to come and giving me the opportunity to be in front of such an august audience, inclusive of colleagues of mine who are far more expert at osteoarthritis than I am, both at the biology or clinical study of such a disease. And I was charged with talking about etiology, pathogenesis, and treatment considerations, some of which you've heard a lot about already, but I'd like to highlight some of the important issues for the non-rheumatologic audience so that perspective can be gained regarding the discussion itself.

There is no question, as you've heard all along, that glucosamine actually has a benefit in the context of an analgesic effect of unclear cause. Whether or not glucosamine is a treatment that actually alters the natural history of the disease, i.e., osteoarthritis, remains entirely debatable and has a lot to do with trial design and outcome measurements. So osteoarthritis as a disease state is what I am actually going to be

talking about.

Typically, it affects people over the age of 50. The slide used to say "elderly," but as I've gotten older, I've obviously had to change that. A biologic process takes place which affects cartilage and, thus, as a result, there's a subsequent inflammatory component that characterizes most of the symptoms and signs of this particular process.

The clinical presentation is pain. Occasionally, patients will show up in my office and complain that, "I can't do what I used to be able to do." But having been a rheumatologist for 25 years, and although I had a boutique practice in an academic environment, I guarantee you I saw plenty of people who came in complaining of pain. And most patients don't come in and say, "I have an osteophyte." They tell me they're uncomfortable and something's wrong with their life.

And if you really look at epidemiologic evidence, it's pretty clear that are large number of patients who are over the age of 75--and I don't

see many of those people around this table, and we talked about this before. But over the age of 75, then a huge number of people, greater than 75 percent, will have X-ray evidence of this process. If you're over 85, 75 percent will be symptomatic. Now that we have more than a million centenarians alive in the United States, some of whom actually pay taxes, this is a very important issue to society. And it probably affects 16 to 20 million Americans, which is also an important issue.

You saw a similar slide to this before, but I'd like to point out that this is looking at the prevalence of all the rheumatic disorders that we consider. And, in fact, osteoarthritis, as you can see, is very frequent. The prevalence is quite high, and it's actually quite important. I'm not entirely sure that neck and back pain does not also reflect a manifestation of osteoarthritis in some circumstances.

So someone has already mentioned this, and I think it's really critical for us to think about this. Although the disease might be something

related to cartilage, the joint is a very complex organ. And the components, the mechanistic components of the joint, are all extremely interrelated. The mechanics of the joint is what we're talking about. So there's cartilage, and cartilage actually is a very interesting tissue. It's predominantly aneural. It's predominantly avascular. it's predominantly alymphatic. And it can represent within the joint two different sources of structure: hyaline cartilage, which is what we think of as the typical cartilage in the joint, consists of predominantly Type II collagen; whereas, fibro-cartilage, which is predominantly Type I collagen genetically, is what makes up other components of cartilage within the joint. Hyaline cartilage is really predominantly only found in the body in the joint--and just as an aside, in some other tissues, but predominantly in the joint.

What it's there for is to cushion and provide a particularly remarkable surface once changed to a degree by certain products such as hyaluronic acid and lubricin that can lead to

almost nearly a frictionless surface to allow motion to take place in very complex areas.

Then there are the menisci. The menisci are also cartilage, and they really consist of Type I collagen. There are other components to hyaline cartilage that we'll talk about in a minute.

Then there are tendons and ligaments, the joint capsulate itself. There's bone. There's actually the periosteum component of bone, and subchondral bone since the 1960s has been considered a very important component of transmission of forces in the normal, everyday use of the joint so that there's cushioning provided by an arcade of Type II collagen within the cartilage, but then the forces are also attenuated through the immediate subchondral bone.

Then there's synovial fluid, which provides nutrition in a certain way, but also some of the aspects that we talked about, about the frictionless surface provided by the components of synovial fluid, inclusive of hyaluronic acid and lubricin. And then the muscles surrounding the

joint, many people are common to say a good athlete, even they may have bad knees, by having excellent musculature can provide a lot of the support. And the evidence has been done over the years that, in fact, you really want to build up the muscles around a diseased joint to provide better support and better symptomatic control.

So here is what we talk about when we think about the idea of the joint as an organ. What I'm looking at here is just the bone, but here is the joint capsule and tendons. Here is the menisci. Here is the joint space. We've already seen and talked a lot about joint space so far. And in here is the hyaline cartilage lining the surface of the bone, which is the articular surface, the portion of the bone that moves through range of motion, predominantly. And you've seen a picture like this before, and these are the molecules of Type II collagen. And interposed between them are very important high-molecular-weight substances, the proteoglycans, that allow cartilage to be extraordinarily well-hydrated. So

there's a lot of water in this substance that leads to a lot of resiliency, a sense of being able to tolerate a lot of sheer stress and to not deform too greatly and be able to retain its format, so to speak.

There are multiple other forms of minor collagens which some people believe may play a very important role in progressive disease in some patients.

So there's been a lot of talk about risk factors for the generation of this disease this morning, most of which have already been actually discussed. Someone asked the question about genetics, and clearly, what we understand about genetics so far is that there are some people that have abnormal components of the joint, and those abnormal components might be, such as in Ehlers-Danlos syndrome, which is a disease of elasticity, a disease that, in fact, can lead to hypermobility because of increased range of motion, or more recently some people have discovered a Type II collagen defect in some families, and there are now

about 16 families in the entire world that actually have this Type II collagen defect, which then leads to a rapid and early form of osteoarthritis. So it's not a very common event compared to the numbers of patients who actually have osteoarthritis.

There's also been a recent identity of a new familial cohort with a form of increased chondrolysis. You get earlier dissolution of collagen and cartilage, and that also has been seen in two family cohorts.

So many of us don't believe that we have found the specific or singular genetic defect that might lead to osteoarthritis, and most of us believe that there is one. It may be eluding us, but there may be multiple different kinds of defects that, if they're genetic, might do that. Or perhaps there's yet an undiscoverable defect in some of the minor collagens that might be associated with the more common form of progressive osteoarthritis.

Then there are congenital anomalies that

are unrelated to these kinds of changes, such as a shallow cup where the acetabulum is in the hip that may lead to premature hip osteoarthritis.

Then there's trauma, and trauma obviously everybody understands that, and it can be quite unique and limited to the post-fracture scenario, the football player, or whatever. Then there are overuse syndromes, and Dr. Felson is an expert in identifying some of those people in Asia, for example, in China, who stoop all the time or who use chopsticks in a certain way that actually might lead to osteoarthritis of those particular joints. It's actually a fascinating phenomenon. The real question which I asked him last night on the plane was whether or not, in fact, if you then changed how they stood or changed how they used the chopsticks, introduced them to a fork, might that actually change the behavior and change, thus, the onset of osteoarthritis? I suspect that Dr. Felson would answer, but he certainly has the opportunity, to suggest that we don't know the answer to that question. And, therefore, some of the questions

that were brought up this morning as alteration of risk factors and that we'll talk about in a minute are clearly unknown.

Then there's a post-infectious state, such as patients who have rheumatoid arthritis or--that's post-inflammatory, or patients who develop some form of streptococcal arthritis or other form of infectious disease of the joint that can lead to destruction of the cartilage and bone and, thus, without replacement might lead to secondary osteoarthritis.

Then many of us have discussed already and thrown out the terminology of obesity, and that clearly has been a risk factor and identified both from the Framingham Study as well as other epidemiologic studies. And now that we're in a Foods Advisory Committee, obviously it's a very important consideration and everybody knows that the epidemic of obesity has been on all of the front pages of all the major scientific journals, such as Newsweek and Time.

So, in fact, there is a clear issue that

obesity plays an important role in the inception and ongoing presence of osteoarthritis, particularly of the lower extremity. The other problem, of course, with obesity is: What does it mean to change it? How do you alter the disease state? Do we actually know that by decreasing weight significantly over a 30- to 40-year period you'll actually change the natural history of the progressive nature of osteoarthritis or change the symptoms, or will you change both? That's really yet to be defined.

There is yet another form of genetic disease that we don't understand which is a patterning of disease, and it's called hereditary osteoarthritis or hereditary osteoarthrosis, and I'll show you some pictures of that. And it's a particular clinical pattern of presentation of nodular osteoarthritis, particularly of the hands. Now, whether or not that is a major focus, I have no idea. I certainly look at my hands, and I remember my mother's hands quite well, and she had that significant event, and yet I have not yet done

that. And she developed it at the age of 50, and I am significantly beyond that. What genes are related to that still elude us.

So many of us try to think of osteoarthritis, knowing what we know--which is light years more than we knew ten years ago, but is still light years less than what we need to do to really understand this process--is we think of it as patients who have either normal cartilage and something happens, or patients who have abnormal cartilage at the inception of their being and something happens. So a very simplistic way to look at that is that the patient with normal cartilage and supporting structures is subjected to abnormally increased loads. And if you think about osteoarthritis as we think about it, it's predominantly in the lower extremity, and it predominantly affects those weight-bearing joints. And yet ankles are not particularly involved in osteoarthritis, and something else is happening in that regard; whereas, knees and hips are. And yet ankles also carry weight, and why that's exactly

sure, we don't know. So obesity and overuse syndromes may be examples of how that is affected.

Then there's the idea of the abnormal cartilage and supporting structures are subjected to either minimal or normal loads or abnormally large loads, and then you can think of inherited defects of structural components like I mentioned, defects of Type II collagen, a cartilage lysis syndrome, hypermobile syndromes. And then there are metabolic disorders that an lead to this where you get deposition of pigment that alters the characteristics of cartilage, such as in ochronosis. And some people believe that maybe even iron changes, as in hemochromatosis, may lead to some abnormalities of cartilage that could lead to these events.

However, the biology of osteoarthritis is actually now being elucidated much more clearly, and I grew up at a time when people actually used the term--and I can remember well training in an arthritis program at a major center, where I was told that osteoarthritis was "degenerative joint

disease," that this was not an inflammatory process, that it was entirely unrelated. And then Dr. Abramson taught me otherwise by convincing me that, in fact, there's an inflammatory process.

Regardless of that, it is a slowly progressive disease, and it's remarkably heterogeneous. Everybody in this room, as we've discussed, is probably at risk in certain ways or another. And if every one of us has this process, I guarantee you we would all progress in different ways based on our own uniqueness.

It's primarily affecting cartilage. There is an early cellular response. And as mentioned before by someone on the other side of the table, early on there's actually increased synthetic capacity at the cartilage, that there is actually an attempt to make more collagen, to make more proteoglycans, there's increased hydration because of that, and it's only subsequently later that, in fact, there seems to be a failure of the chondrocyte, the cell that's responsible for maintaining cartilage, that there's a failure of

the chondrocyte in its ability to actually make all of these things, and then you get progressive disease.

T8 Well, that's all well and good. It's all phenomenological. But whether there's actually any proof that those changes are truly related to the evolution of progressive disease is unknown.

And where inflammation begins to play a role in actually how this all evolves is very debatable. So you saw evidence by the Pelletiers and others that have been suggested that IL-1 and TNF alpha, two important cytokines that are primarily involved in rheumatoid arthritis, are involved here is true. But what their involvement and how important it is from a causality point of view is entirely unknown.

There is absolutely no question that synovial hypertrophy takes place in this disease. However, the extent of synovial hypertrophy is much less than you get in proliferative autoimmune disease such as rheumatoid arthritis. So with this hypertrophy, with this cellular change, we know

that inflammation is important. Exactly how important is unknown. And although it has been alluded to already that this may be a systemic process, it's not systemic in the nature of systemic like rheumatoid arthritis. It's systemic in the fact that whatever the abnormality to cartilage, whatever the abnormalities are that predispose this progressive nature, is inherently there. The systemic nature is not that there's a lot of inflammation so that you can measure a systemic response with CRP. So basically most of us would argue that this is actually a local event.

So, in fact, something happens at the cellular level which then leads to structural change, and you saw some pictures of that earlier. And then there's pain and other signs and symptoms that come along here. And I will reiterate this throughout my talk. There are plenty of people that have X-ray evidence of change and have no pain or symptoms. Do those people actually have osteoarthritis? Conversely, hardly anybody has osteoarthritis if they have symptoms and don't have

any change, as evidenced by an imaging technology that can help us make a diagnosis. But a diagnostic X-ray doesn't make the diagnosis. It is a supportive diagnosis of a clinical state as manifested how the patient presents. And that is ascertained by pain, functional limitations, and then obviously reduced health-related quality of life, which can then lead to actually the ultimate intervention, although I'm not a surgeon, of surgical intervention.

I love these dynamic slides.

So basically the pattern of joint involvement tells us something, but as a rheumatologist, because we have no--and it's already been ascertained, we have no specific blood test that tells us about a diagnosis, we have no specific ascertainment system, so we base it on clinical presentation. The asymmetry of joint involvement is very important and an overall way to look at somebody who shows up with pain and which joints are involved.

So to show you the dilemma--perhaps

rheumatology remains the last bastion of the diagnostician--basically you get certain joints that are involved and not other joints involved. So most people don't think that the MCPs, the metacarpal phalangeal joints, are typically involved in osteoarthritis, and that the DIPs, the distal interphalangeal joints, and the proximal interphalangeal joints are those that are more commonly associated when the hand is involved. Furthermore, the first cup or metacarpal is where at the base of the thumb, people think of this as a pretty traditional place, big toe, knee, hip, lower back, and neck, but not typically the thoracic spine. So it probably has something to do with the kind of plumb line that goes on with the body and where pressure relationships and weight-bearing or load-bearing takes place. Those of us who think about this a lot see a patient who presents with shoulder osteoarthritis, you think about a football player or some other form of trauma. Elbow osteoarthritis is considered incredibly rare without trauma, as well as wrist osteoarthritis.

So why is that? These are all diarthrodial joints. They all have synovial lining. Why are certain ones affected and not others? Furthermore, to contrast that, in rheumatoid arthritis the DIPs are almost never involved. So, unfortunately, the patterning of disease is important, and, unfortunately, without any other kind of biologic markers, were quite at risk. So the diagnosis of osteoarthritis is dependent upon several particular issues and, as mentioned, it's predominantly symptoms of pain, decreased function, or both, and you can see that with decreased function due to bony change, due to soft-tissue change or swelling, or due to alterations of the normal structures that can lead to change, some of which you can actually feel or sometimes even hear when a patient walks in with crepitance, and the crepitance is actually pieces of cartilage and bone within the joint space itself. We actually call those "joint mice," interestingly enough.

Then the other signs that can actually up

on physical examination include the asymmetry of the findings, the involvement of usually the large joints, something called Heberdens and Bouchard's nodes, which we'll talk about in a minute, which are the classic hand involvement of the distal and proximal interphalangeal joints with actually bony nodules, hypertrophy of the bony structure there associated most commonly with decreased joint space. Exactly what came first is still debatable. Bony swelling, some swelling and pain out of proportion sometimes to the inflammatory findings.

This picture, obtained from the American College of Rheumatology slide collection, is a classic example of bony involvement with Heberdens and Bouchard's nodes of the hand. Now, someone asked a question about the non-involved joint in this construct, and it has already been alluded to that likely the joints would be affected in some way, but they may not manifest themselves in this total manner. Not everybody has to have symmetrical disease with this form of presentation, and why the node is not in this middle finger

compares to this fourth finger is entirely unknown. And why one is more inflammatory than another without trauma, banging it, or whatever, is entirely unknown. So because of that, there's a lot that's unknown.

Furthermore, you can actually see this involvement here of the first cup or metacarpal with what we call squaring and an actual movement of the joint this way and can lead to significant alterations in function.

Then there's the imaging technology which is, in fact, becoming much more robust and mature with the development of magnetic resonance imaging. But basically, to date, the standard of imaging has been X-ray, looking either for the presence of osteophytosis, which theoretically and phenomenologically is thought to be biologic evidence of an attempt to repair, the idea that the mechanics of what's going on has led to hypertrophic change and new bone formation. Exactly whether that's true or not is entirely up to supposition.

Progressive joint space narrowing has always been mentioned throughout the entire morning, and it is a surrogate measure, we believe, of cartilage thinning. There may be other reasons for this to be taking place, such as mentioned with pseudo-widening. But, in general, most often it's associated with actual change in cartilage. And that's because cartilage is not well imaged by the X-ray. It is not dense enough to show up like bone is. And, therefore, it's not just space. There's not a lot of wasted space in the body. And it's not just open space. It's occupied by something.

But the problem, of course, is that this joint space narrowing is entirely difficult to predict. It is non-linear. It is believed that if you take an inception cohort of patients who actually have an evidence of osteophytosis and you actually study them over a several-year period--and there are several databases now to show this--only a small percentage, less than 10 percent, will within a two-year period show rapid change, such change enough to warrant a clinical study. By far,

the majority of the patients will have a slow progression and may not show enough change within two years to actually show a difference in a therapeutic intervention that might actually inhibit joint space narrowing.

So unless we can figure out some methodology to identify those patients who are going to have rapid change propensity, we're going to have a very difficult time studying that patient population for disease modification.

Then the idea of change in the subchondral bone has been unbelievably controversial because we don't know whether it's causal, so that if there are microfractures or there's edema, whatever that is, or if there is some other form of change such as localized osteoporosis due to the low-grade inflammation or disuse or change in weight-bearing or change in the function of the joint, that might lead to these microfractures and a change of transmission of forces, which then might lead to more forces being sustained on the cartilage, and might lead to new cartilage change. We don't know

if it's a causal event or it's a response to change in the cartilage. But when it's present, it clearly identifies a person who will have a moderate to mild inflammatory process that could be considered osteoarthritis.

So these are X-rays that show the example of what we've just talked about with increased bony sclerosis in the subchondral bone, joint space narrowing, as well as the development of osteophytosis, as well as some cysts that are considered important for association with osteoarthritis and malalignment.

So the imaging has been more sophisticated now with MRI, much more expensive; it's able to provide a 3D image of the joint as an organ, much better than the 2D image presented by X-rays. It also can help us understand this joint space that, prior to this, by X-ray is not clearly understood. And we can actually get an approximation of the volume of cartilage. So, therefore, in the future, I may be up here, if you ever invite me back, talking about this issue of cartilage volume rather

than joint space narrowing, a much more quantitative way of looking at this change. And it may be more indicative of the real effect of osteoarthritis. It may be able to identify early change in cartilage metabolism, and Dr. Felson and others were some of the first people to identify a change by MRI in the subchondral bone that initially was called bone edema, and now we know is not, and is probably related somehow a significant change in bone metabolism related to perhaps the inflammation going on in cartilage in that joint and perhaps related to the transmission of forces and perhaps something related to a change within the bone itself, perhaps due to microfractures or other change that's been induced by the change in cartilage.

We've also heard comments about biochemical markers. Well, I actually spent 15 years at the bench at Harvard studying biochemical markers, and I got out of it because I didn't see any future in it--not to suggest there may not be a future in it, but I certainly couldn't justify it

at that point in time.

In that context, there's plenty of sources for markers, because I've mentioned to you, although Type II collagen is predominantly in hyaline cartilage of the joint, there are other sources of Type II collagen; and, thus, epitopes that are related to synthesis or metabolism of Type II collagen may be sourced elsewhere besides the joint.

If, in addition, the joint is only affected in one place in the body, how do we know that what we're measuring that's systemic has anything related to that particular joint unless we're just measuring something in the joint fluid related to that joint? So it could be in the joint tissue or fluid, and you might find synthetic products of the components of the joint or products that reflect metabolism of the components of the joint. It could be found in blood circulating in serum, and it could be products of cartilage turnover, but which cartilage and from where and why?

It could be found in urine, and ideally that would be a nice way to do that. I did spend a lot of time doing that for bone, and there still isn't a blood or urine test for the diagnosis of osteoporosis.

The products of cartilage metabolism which are cleared by the liver or elsewhere, perhaps by the kidney, from the serum and then possibly further processed and then excreted in the urine. Obviously, this is a very promising way to go, but very frustrating. The biochemical markers are not yet adequate for diagnosis of osteoarthritis. It isn't yet adequate for identifying patients at risk or measuring outcomes, but they may be useful in exploratory studies, perhaps more so if we make them more robust. They may help identify at-risk or resistant patients, but not yet. They may help compare therapies, but not yet. They may help patients and doctors select and monitor therapies, but not yet. And it may help assess efficacy, it might be a surrogate endpoint, but not yet.

So what is an early marker versus what is

a surrogate? You've heard a lot of comments about this. Having been at the agency, I'm going to give you the definition of that, not because I continue to be responsible for what the agency says, but nobody had to check my slides, so I can be pretty clear about what the agency actually says.

A biomarker--biological marker--or imaging marker is a characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. It's important to remember that a clinical endpoint--I know you're going to know this, but, nonetheless, it's important to remember that it's a characteristic or variable that measures how a patient feels, functions, or survives. So, therefore, we're really talking about an intervention that might change someone's life, not just changing somebody's X-ray. It has to be symptomatically based. So a VAS scale for pain; a functional outcome in osteoarthritis such as a WOMAC or a HAQ; a patient global assessment. In

all ways, how has this therapy affected you in the last 24 hours?

A surrogate endpoint is a marker that is intended to substitute for such a clinical endpoint. So a surrogate endpoint, according to Bob Temple in 1995--and Bob Temple, for those that don't know, is the doyen of the FDA. Basically, a surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives; changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Well, unfortunately, we have no surrogate markers in the context of osteoarthritis, and, in fact, if someone was to ask me whether we actually have any surrogate markers in any rheumatic disease, I will tell you not. And I have had a lot of involvement in thinking about those in other diseases besides osteoarthritis. What we're left

with are clinical endpoints, and those clinical endpoints are the definition of a therapeutic response.

So I have actually been asked by the people at the FDA to answer specific questions that were posed to me as it relates to what you are considering based on what I've just presented. And I haven't even gone into the variability of an inception cohort versus a progressive cohort--the variability, as mentioned this morning that Dr. Felson said, about the differences in the risk factors associated with incident disease versus progressive disease. And that's because they are not yet totally understood or defined, and only people at Dr. Felson's level actually deal with them at this point in time. We don't know that Vitamin D actually truly plays an important role in progressive disease is osteoarthritis. And we really don't know what the role of obesity is from a causality point of view. But we do know associations.

So what valid modifiable risk factors or

surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? I gave you a list before of those risk factors as we understood them, and one example is obesity. This gives us a clear opportunity to enrich a study with more chance of having progressive disease by recruiting patients who are obese, and that has been shown by Ken Brandt's study of the metalloproteinase inhibitor, and that is shown by a recently publicized trial that failed of bisphosphonate in the treatment of progressive osteoarthritis as measured by X-ray outcome.

So, clearly, we can do something with the obese population and understand more about how to study a population by including obese patients. But, unfortunately, would I use it as a surrogate endpoint? No.

The other problem, of course, is what I mentioned, the low percentage of patients with progressive disease without evidence of actually incident or incipient disease.

So now what valid modifiable risk factors

or surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? Again, we know something about risk factors, patients with repetitive use syndromes, patients who are obese. What do we know about surrogate endpoints? Well, joint space narrowing is evidence of progressive osteoarthritis in most circumstances, but may or may not be associated with an important clinical component of symptomatology. We've already talked about that. Other observed X-ray changes are useful for diagnosis, but are not important by themselves without clinical symptoms of disease. So, unfortunately, really, it's not a surrogate marker.

There are no valid surrogate biochemical markers at this time, so the answer would have to be: What valid surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? None. What valid modifiable risk factors are there? Several risk factors. And they're modifiable, but that's for osteoarthritis as a disease that's symptomatically defined.

The other question asked was: Are joint degeneration and cartilage deterioration signs or symptoms of osteoarthritis? Well, yes. In the absence of another explanation such as ongoing systemic inflammatory disease or other things, there is evidence in the context of the symptoms of osteoarthritis that joint degeneration and cartilage deterioration is a sign.

Are joint degeneration and cartilage deterioration modifiable risk factors/surrogate endpoints for osteoarthritis? I would say not generally. The presence of the above finding are part and parcel to osteoarthritis. Joint space narrowing may be an important way to demonstrate that a structure-modifying drug may be active, but if there's to be improvement in the structure, it would be expected at some time that there might be a linked improvement in symptoms. If, in fact, that would happen, then joint space narrowing or progressive joint space narrowing might be a surrogate marker for that, but no one has ever seen that yet. And, in fact, as based on the draft

guidance document in osteoarthritis, generated by the FDA in the year 2000, it might be difficult to prove that. How long would you wait for a symptom change would take place in association with change in joint space narrowing?

So patients present with pain or other symptoms. Joint change and cartilage deterioration in some patients may be associated with pain and loss of function, but not all patients will have symptoms in the context of the observed change. Once a patient has pain, he will likely have evidence of change. But not all patients with change have symptoms, and that it's a spectrum of disease has already been suggested. But, in fact, is it a spectrum of natural degenerative process? Is it a spectrum of aging? Is Alzheimer's a spectrum of aging or is it a disease? Is lack of memory all Alzheimer's, or do people who get older sometimes become forgetful without Alzheimer's? And it's already been mentioned about LDL, HDL, hypertension, and other issues. Complicated.

So without--with, you know, talking about

osteoarthritis, you can't finish a talk without talking about therapy, and I was asked to also talk about therapy as it stands today. And basically as it stands today, it's designed to improve modifiable risk factors, so you reach ideal body weight in those that are obese. I have never actually achieved that in any of my patients. And as you can see, I have not achieved that in myself. Decreasing body weight probably does provide a decrease in symptoms. Do you alter lifestyle behavior such as associated with overuse syndromes? Jackhammer operators will tell you that they have to operate a jackhammer so they can bring food to their table. So it's not clear that you can always achieve that kind of behavior in an overuse syndrome. I'm not sure that Dr. Felson is going to be able to change the Chinese behavior of using chopsticks.

Now, in addition, we want to make patients feel better. We don't have anything that alters the natural history of the disease. So we use palliative therapy to decrease symptoms of pain,

leading hopefully to an improved health-related quality of life that's measurable either through some health assessment questionnaire or an SF-36 or other modality in a clinical trial. And by coming into the office to see your physician, answering the question, "How do you feel today?" with "I'm feeling much better." That's the inclusive use of analgesics and anti-inflammatory therapies, use of assistive devices to unload joints, use of cognitive behavioral therapy, and use of physical function and exercise therapy. There are yet no proven structure-modifying therapies, although there is some evidence recently that perhaps using a metalloproteinase inhibitor such as doxycycline in the right patient might make a difference, but that needs to be corroborated by larger studies and other studies.

I think I'm one of the few people in the United States or around the world that has actually participated in a double-blind, controlled trial of magnets, for example, that's recently been published. And, in fact, magnets don't work. And

you'll notice up here that I haven't said what I mean by analgesic or anti-inflammatory drugs.

I am co-Chair of the Steering Committee of a group called OMERACT, which is the Outcome Measures used for Rheumatic Disease Clinical Trials. OMERACT has been around for some time, and it defined what were the core outcome measures based on consensus that one would use in the study of osteoarthritis in randomized controlled trials. And basically what it showed--and by consensus of several hundred people interested in this field--that measuring pain, measuring physical function as opposed to disability, measuring a response to a patient global question, measuring imaging change over one year are the key important issues associated with ascertaining improvement in osteoarthritis, that biologic markers are way out here in the periphery, only because they're experimental as of yet, that the issue of stiffness is very controversial; that measuring characteristic markers of inflammation is hard to know what to do; that perhaps it will be important

to look at numbers of flares in an intermittent process; perhaps it's important to think about a fundamental and ultimate clinical outcome of altering the time to surgical replacement or other form of surgical procedure; and then perhaps also concomitant therapy where you use two or three therapies together and you measure the effect of an anti-inflammatory, an analgesic, based on how much rescue analgesic that they may use.

I have chosen to show you two different bits of data about where benefit lies and how much benefit a patient might see in a clinical trial using anti-inflammatory drugs. In 1991, Ken Brandt and others, in an article in the New England Journal, suggested that acetaminophen should be the first-line therapy, up to 4000 milligrams a day, to treat these patients for symptomatic osteoarthritis. Many of us have felt that with the evolution of an understanding that this is an inflammatory process, that that may not be enough. So this is actually a slide and a study looking at the use of two different COX-2 inhibitors head to

head versus placebo over a six-week period in patients who have flared osteoarthritis. And what I show here is not the fact that these drugs work. I actually show that the placebo works very well in this process for an acute benefit of pain over a several-week period. And, furthermore, the effect size of what a COX-2 inhibitor or a non-selective nonsteroidal may attain in this kind of expression is not overwhelming, that about 35 percent of the patients get 35 percent better with an anti-inflammatory/analgesic.

If you look at function--and this is measured by the Western Ontario and McMaster Analysis, which is, in fact, what most people use in determining outcome in osteoarthritis, you also see that there's a dramatic placebo response, but based on the size of the trials, there's statistical significance and change between what placebo brings to the table versus what is measurable by a nonsteroidal anti-inflammatory drug, in this context, selective COX-2 inhibitors.

However, Pincus and others--and I am

actually an author on this--have actually shown some very interesting evidence in a crossover trial which has its own problems, which we don't need to go into. But basically what they have shown is--and other people have suggested this as well, Fred Wolfe and others--that patient preference prefers the use of anti-inflammatory drugs rather than simple analgesics alone. This is actually two--

DR. MILLER: Dr. Simon, excuse me. Could you begin to summarize, please?

DR. SIMON: Yes, I'm almost done. There are two separate trials here, and basically they show in this context a nonsteroidal versus acetaminophen versus placebo, that there's actually much significant improvement with the nonsteroidal-like drug than the simple analgesic alone; and, most importantly, that patients clearly appreciated the effects of the anti-inflammatory drug over acetaminophen, whether you look at it in the context against placebo or against the acetaminophen directly.

So in that context, and in conclusion, I

think it's important for us to recognize that this is a heterogeneous disease with not a hell of a lot of understanding about the biology and where we're going. We have a process which is difficult to quantify, a process that's very difficult to study, a process where we have no structure-modifying therapies, that basically what we can really attain in a therapeutic approach is to make patients feel better. How to prevent this process without really understanding the basic biochemical, biologic changes that induce it remains elusive. And whether or not we will ever be able to answer that within my lifetime remains unclear.

So thank you very much for the time, and I appreciate being here.

[Applause.]

DR. SIMON: Thanks for the clap.

DR. MILLER: You have friends.

Any comments or questions? Dr. Krinsky?

DR. KRINSKY: I feel I'm beating a dead horse, but you have a slide that says, "A spectrum of disease, mild disease is still disease and